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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,144	TZERTZINIS ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *11 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 14, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed August 15, 2008.

Claims 1-18 are pending in the instant application.

Election/Restrictions

Applicant's Election of Group I, claim 10 and linking claims 1-9 and 11-14 in the reply filed on August 15, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, after careful reconsideration of the claims, a new restriction requirement is made of record as detailed below. It is noted that the instant restriction requirement replaces the previous restriction requirement mailed July 18, 2008. In this regard, Applicant's Election of Group I filed August 15, 2008 is moot.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 10, drawn to composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, wherein the targeted gene encodes Erk1, classifiable in class 536, subclass 24.5, for example.

II. Claim 10, drawn to composition comprising a plurality of dsRNA fragments

having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, wherein the targeted gene encodes Erk2, classifiable in class 536, subclass 24.5, for example.

III. Claim 11, drawn to composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, wherein the targeted gene encodes Ffluc luciferase, classifiable in class 536, subclass 24.5, for example.

IV. Claim 11, drawn to composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, wherein the targeted gene encodes Renilla luciferase, classifiable in class 536, subclass 24.5, for example.

V. Claim 15, drawn to a method of preparing a composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, comprising transcribing at least

one RNA molecule having a sequence identity with a portion of a target gene, to form a large dsRNA; cleaving the large dsRNA by means of RNase III or mutants thereof; determining whether the large dsRNA can silence gene expression of the target gene in COS cells, and obtaining the composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, classifiable in class 435, subclass 6, for example.

VI. Claims 16-18, drawn to a method of silencing gene expression comprising cleaving with an enzyme, a dsRNA having sequence identity with a target gene, wherein the enzyme is RNase III or a mutant thereof and the cleavage product is a set of overlapping fragments of dsRNA; transfecting cells with the cleavage product, and obtaining silencing of expression of the target gene, classifiable in class, classifiable in class 514, subclass 44, for example.

Claims 1-9 and 12-14 links the invention of Groups I-IV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claims, claims 1-9 and 12-14. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any

such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct, each from the other, because of the following reasons:

Groups I-IV are related to Group V as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the compositions comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells of Groups I-IV can be used in materially different process such as a hybridization probe in a method of identifying target gene expression *in situ*, which is a materially different process than the method of silencing gene expression comprising cleaving with an enzyme, a dsRNA having sequence identity with a target gene, wherein the enzyme is RNase III or a mutant thereof and the cleavage product is a set

of overlapping fragments of dsRNA of Group V. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the Examiner if restriction were not required because the inventions require a different field of search (see MPEP 808.02), restriction for examination purposes as indicated is proper.

Group V is drawn to a method of preparing a composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells, comprising transcribing at least one RNA molecule having a sequence identity with a portion of a target gene, to form a large dsRNA; cleaving the large dsRNA by means of RNase III or mutants thereof; determining whether the large dsRNA can silence gene expression of the target gene in COS cells, and obtaining the composition comprising a plurality of dsRNA fragments having overlapping sequences, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein the composition is capable of specifically silencing expression of a target gene in COS cells and is considered to be distinct from the method of silencing gene expression comprising cleaving with an enzyme, a dsRNA having sequence identity with a target gene, wherein the enzyme is RNase III or a mutant thereof and the cleavage product is a set of overlapping fragments of dsRNA; transfecting cells with the cleavage product, and obtaining silencing of expression of the target gene of Group VI. The inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive;

the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the method of Group V is distinct from the method of Group VI since the method of Group V recites distinct method steps and distinct objectives, apart from the method steps and objectives recited in Group VI. Furthermore, Group V is distinct from Group VI since the invention of Group V does not overlap in scope with that of Group VI since each Group recites materially distinct methods which differ in criteria for success. Because these Groups utilize unique and different method steps, the inventions are also therefore not obvious variants, and have a materially different design. Furthermore, because these Groups utilize unique and different method steps, the prior art applicable to one Group would not likely be applicable to another Group and the inventions in each Group are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. Accordingly, restriction between these Groups is considered proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper. Also, because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the Examiner if restriction were not required because the inventions require a different field of search (see MPEP 808.02), restriction for examination purposes as indicated is proper.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37

CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Applicant's Representative, Harriet M. Strimpel, on or around September 12, 2008, a provisional election was made to prosecute the invention of Group I, claim 10 and linking claims 1-9 and 12-14. Affirmation of this election must be made by Applicant in replying to this Office action.

Accordingly, claims 11 and 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Additionally, Erk2 as recited in claim 10 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made during the telephonic conversation on or around September 12, 2008.

Claims 1-10 and 12-14 and Erk1 as recited in claim 10 have been examined on the merits.

The restriction requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Applicant's information disclosure statement filed August 14, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Drawings

The Drawings filed August 14, 2006 are acknowledged and have been accepted by the Examiner.

Priority

The reference to priority in the first line of the specification is acknowledged. It is noted that the instant application is the national stage entry of PCT/US2005/004409. It is also noted that certified copies of the priority document have been received in this national stage application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 12-14 are rejected under 35 USC 102(b) as being anticipated by Yang et al. (Applicant's Reference CU on the information disclosure statement filed August 14, 2006).

Claim 1 is drawn to a composition comprising a plurality of double-stranded RNA (dsRNA) fragments having overlapping sequences, each fragment having a size in the range of 18-30 nt, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells. Claim 2-9 and 12-14 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein the composition is capable of specifically silencing expression of a target gene by at least 70% or 80%; wherein the dsRNA has a size of at least 100-nt; wherein the plurality of fragments is at least 5 fragments or 10 fragments; wherein the large dsRNA has a sequence identity with a first portion of a mRNA sequence such that the plurality of the dsRNA fragments derived therefrom has a greater gene silencing activity at less than 2mM than a second plurality of fragments having sequence identity with a second portion of the mRNA; wherein the plurality of dsRNA fragments have a greater gene silencing activity at the concentration of less than 2nM than any single fragment in the composition; wherein the enzymatic digestion is achieved using RNase III or a mutant RNase III in a manganese buffer; wherein the fragments are derived from digestion of a plurality of dsRNAs and wherein the plurality of dsRNA have sequence identity with non-contiguous regions of the mRNA; wherein

the fragments are derived from digestion of a plurality of dsRNA wherein the plurality of dsRNA has a sequence identity with contiguous regions of the mRNA; and wherein 1nM of the composition is capable of silencing gene expression by at least 70%.

Yang et al. disclose the use of *E. Coli* RNase III to cleave long dsRNA into siRNA. It is noted that the siRNA generated are approximately 25 nucleotides in length and mediate sequence specific gene inhibition in mammalian cells (see Abstract, Figure 1, and pages 9943, second column and 9944, first column, for example). It is noted that the cleavage reactions were carried out in the presence of M_gCl_2 (see page 9943, first column, for example).

It is noted that Yang et al. do not necessarily teach wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells or wherein 1nM of the composition is capable of silencing gene expression by at least 70% as recited in Applicant's claimed invention. However, Applicant is reminded that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this instance, the siRNA which mediate sequence specific gene inhibition in mammalian cells disclosed by Yang et al. are capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells and are capable of silencing gene expression by at least 70% as recited in Applicants' claims. Therefore, the siRNA meet the functionality as recited in the instant claims.

Therefore, absent evidence to the contrary, Yang et al. anticipate claims 1-9 and 12-14.

Claims 1-9 and 12-14 are rejected under 35 USC 102(b) as being anticipated by Myers et al. (Applicant's Reference CL on the information disclosure statement filed August 14, 2006, Epub date 2003 Feb 18).

Myers et al. disclose that pools of 20- to 21-base pair siRNAs can be produced enzymatically *(in vitro)* using recombinant Dicer, an RNase III enzyme (see, for example, Abstract and Figure 1). Myers et al. disclose that Dicer-generated siRNAs are effective in silencing target gene expression in mammalian cell culture (see Abstract and Figure 2, for example). It is noted that the Dicer cleavage reactions were carried out in the presence of M_gCl_2 (see page 327, second column).

It is noted that Myers et al. do not necessarily teach wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells or wherein 1nM of the composition is capable of silencing gene expression by at least 70% as recited in Applicant's claimed invention. However, Applicant is reminded that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this instance, the siRNA which silence target gene in mammalian cells as disclosed by Myers et al. are capable of specifically silencing expression of a target gene by at least

65% in transfected COS cells and are capable of silencing gene expression by at least 70% as recited in Applicants' claims. Therefore, the siRNA meet the functionality as recited in the instant claims.

Therefore, absent evidence to the contrary, Myers et al. anticipate claims 1-9 and 12-14.

Claims 1-9 and 12-14 are rejected under 35 USC 102(b) as being anticipated by Donzé et al. (Applicant's Reference CC on the information disclosure statement filed August 14, 2006).

Donzé et al. disclose that long dsRNA can generate siRNA *(in vitro)* by cleavage with T7 RNA polymerase (see, for example, Abstract and Figure 1). Donzé et al. disclose that T7-siRNAs are effective in silencing exogenous and endogenous target gene expression in mammalian cell culture (see Abstract and Figures 2 and 3, for example). It is noted that transcription reactions were carried out in the presence of M_gCl_2 (see page 1 of 4, second column).

It is noted that Donzé et al. do not necessarily teach wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells or wherein 1nM of the composition is capable of silencing gene expression by at least 70% as recited in Applicant's claimed invention. However, Applicant is reminded that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the

prior art structure is capable of performing the intended use, then it meets the claim. In this instance, the siRNA which silence target gene in mammalian cells as disclosed by Donzé et al. are capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells and are capable of silencing gene expression by at least 70% as recited in Applicants' claims. Therefore, the siRNA meet the functionality as recited in the instant claims.

Therefore, absent evidence to the contrary, Donzé et al. anticipate claims 1-9 and 12-14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being

unpatentable over either Yang et al. (Applicant's Reference CU on the information disclosure statement filed August 14, 2006, Myers et al. (Applicant's Reference CL on the information disclosure statement filed August 14, 2006, Epub date 2003 Feb 18), or Donzé et al. (Applicant's Reference CC on the information disclosure statement filed August 14, 2006) in view of Fisher et al. (Atherosclerosis, 2001 Vol. 156:289-295).

Claim 1 is drawn to a composition comprising a plurality of double-stranded RNA (dsRNA) fragments having overlapping sequences, each fragment having a size in the range of 18-30 nt, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells. Claim 2-9 and 12-14 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein the composition is capable of specifically silencing expression of a target gene by at least 70% or 80%; wherein the dsRNA has a size of at least 100-nt; wherein the plurality of fragments is at least 5 fragments or 10 fragments; wherein the large dsRNA has a sequence identity with a first portion of a mRNA sequence such that the plurality of the dsRNA fragments derived therefrom has a greater gene silencing activity at less than 2mM than a second plurality of fragments having sequence identity with a second portion of the mRNA; wherein the plurality of dsRNA fragments have a greater gene silencing activity at the concentration of less than 2nM than any single fragment in the composition; wherein the enzymatic digestion is achieved using RNase III or a mutant RNase III in a manganese buffer; wherein the fragments are derived from digestion of a plurality of dsRNAs and wherein the plurality

of dsRNA have sequence identity with non-contiguous regions of the mRNA; wherein the fragments are derived from digestion of a plurality of dsRNA wherein the plurality of dsRNA has a sequence identity with contiguous regions of the mRNA; wherein 1nM of the composition is capable of silencing gene expression by at least 70%; and wherein the target gene encodes Erk1.

Determining the scope and contents of the prior art

Yang et al. teach the use of *E. Coli* RNase III to cleave long dsRNA into siRNA. It is noted that the siRNA generated are approximately 25 nucleotides in length and mediate sequence specific gene inhibition in mammalian cells (see Abstract, Figure 1, and pages 9943, second column and 9944, first column, for example). It is noted that the cleavage reactions were carried out in the presence of M_gCl_2 (see page 9943, first column, for example).

Myers et al. teach that pools of 20- to 21-base pair siRNAs can be produced enzymatically *(in vitro)* using recombinant Dicer, an RNase III enzyme (see, for example, Abstract and Figure 1). Myers et al. disclose that Dicer-generated siRNAs are effective in silencing target gene expression in mammalian cell culture (see Abstract and Figure 2, for example). It is noted that the Dicer cleavage reactions were carried out in the presence of M_gCl_2 (see page 327, second column).

Donzé et al. teach that long dsRNA can generate siRNA *(in vitro)* by cleavage with T7 RNA polymerase (see, for example, Abstract and Figure 1). Donzé et al. disclose that T7-siRNAs are effective in silencing exogenous and endogenous target gene expression in mammalian cell culture (see Abstract and Figures 2 and 3, for

example). It is noted that transcription reactions were carried out in the presence of M_gCl_2 (see page 1 of 4, second column).

Neither Yang et al., Myers et al., nor Donzé et al. teach wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells or wherein 1nM of the composition is capable of silencing gene expression by at least 70% as recited in Applicant's claimed invention. However, Applicant is reminded that the recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this instance, the siRNAs taught by either Yang et al., Myers et al., or Donzé which silence target gene expression in mammalian cells are capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells and are capable of silencing gene expression by at least 70% as recited in Applicants' claims, absent evidence to the contrary.

Ascertaining the differences between the prior art and the claims at issue

Also, neither Yang et al., Myers et al., nor Donzé et al. teach wherein the target gene encodes Erk1.

Fisher et al. teach the desire to target Erk1 with antisense nucleotides which are capable of silencing target gene expression (see Abstract and page 290, second column, for example).

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to make a composition comprising a plurality of double-stranded RNA (dsRNA) fragments having overlapping sequences, each fragment having a size in the range of 18-30 nt, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells using the teachings of either Yang et al., Myers et al., or Donzé et al. It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to have the target gene encode Erk1 using the teaching and motivation of Fisher et al.

One of ordinary skill in the art would have been motivated to make a composition comprising a plurality of double-stranded RNA (dsRNA) fragments having overlapping sequences, each fragment having a size in the range of 18-30 nt, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells since Yang et al., Myers et al., and Donzé et al. teach that such a composition could be used to silence target gene expression in mammalian cells. One of ordinary skill in the art would have been

motivated to have the target gene encode Erk1 because Fisher et al. taught the desire to inhibit Erk1 gene expression which subsequently inhibits proliferation in mammalian cells.

One of ordinary skill in the art would have had a reasonable expectation of success of making a composition comprising a plurality of double-stranded RNA (dsRNA) fragments having overlapping sequences, each fragment having a size in the range of 18-30 nt, wherein the composition is formed by enzymatic digestion of one or more large dsRNAs and wherein less than 2nM of the composition is capable of specifically silencing expression of a target gene by at least 65% in transfected COS cells since Yang et al., Myers et al., and Donzé et al. taught the successful use and design of such a composition. One of ordinary skill in the art would have had a reasonable expectation of success of having the target gene encode Erk1 since Fisher et al. taught that the Erk1 gene could be successfully targeted using a nucleic acid inhibitor of gene expression.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758.

The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James “Doug” Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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September 20, 2008
/Terra Cotta Gibbs/